Supplementary Methods

Study Population

The study population comprised participants in the case-control study Sahlgrenska Academy Study on Ischemic Stroke (SAHLSIS), the design of which has been reported.[1] Briefly, European ancestry adults aged 18–69 years ($n = 600$) who presented with first-ever or recurrent ischemic stroke were recruited consecutively at four stroke units in western Sweden between 1998–2003. Controls ($n = 600$) included in SAHLSIS were matched to cases for age (+/− 1 year), sex and geographic area of residence and were randomly selected from a population-based health survey or from the Swedish Population Register as described.[1] Control subjects were excluded if they had a history of atherothrombotic disease. All patients underwent neuroimaging and were examined by a physician trained in stroke medicine at admission and at follow-up after three months.

The Malmö Diet and Cancer Study (MDC) is a population-based cohort study.[2] Between 1991 and 1996, 11,246 men and 17,203 women, born between 1923 and 1950, were included and underwent baseline examinations. Incident stroke diagnoses occurring after baseline, as well as prevalent stroke diagnoses (before baseline), were ascertained in the Stroke register of Malmö.[3] A few incident stroke diagnoses occurring in hospitals outside of Malmö, and prevalent stroke diagnoses occurring before 1989, were retrieved from the Swedish National Hospital Discharge Register.[4] For the present study, 248 individuals with prevalent IS, or incident IS occurring until Dec 31 2008 were included. The remaining samples comprised control individuals without stroke until Dec 31 2008, that participated in a randomly selected subcohort of the MDC (the MDC Cardiovascular Cohort) ($n = 1812$). Given venous blood samples were isolated at baseline, prior to the manifestation of atherothrombotic disease, all MDC samples ($n = 2,060$) were treated as controls in the genetic analyses.

Stroke Definition and Vascular Risk Factors

Stroke was defined in accordance with the definition by the World Health Organization.[5] Ischemic stroke was diagnosed when clinical findings were consistent with stroke and brain imaging excluded other causes, e.g., hemorrhage and non-vascular diseases.

Sample characteristics, data collection and clinical definitions for SAHLSIS and MDC have been described.[1,2] Hypertension was defined by pharmacological treatment for hypertension, systolic blood pressure (SBP) $\geq$ 160 mm Hg, and/or diastolic blood pressure (DBP) $\geq$ 90mm Hg. Diabetes mellitus was defined by diet or pharmacological treatment, fasting plasma glucose $\geq$ 7.0 mmol/L, or fasting blood glucose $\geq$ 6.1 mmol/L. Hyperlipidemia was defined as pharmacological treatment, total fasting serum cholesterol level > 5.0 mmol/L, and/or LDL > 3.0 mmol/L. Smoking habit was coded as current versus never or former (smoking cessation at least one year before inclusion in the study). High sensitive CRP was determined as described previously (SAHLSIS[6]; MDC,[7]). For SAHLSIS, information regarding vascular risk factors was registered once in controls and at the 3-month follow-up in patients. For MDC, this information was collected at baseline.

### Supplementary References

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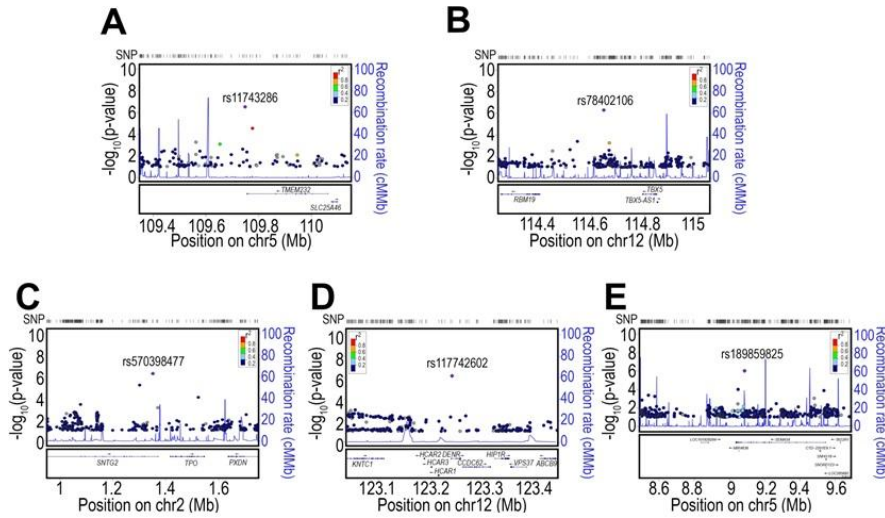
Supplementary Figure S1 Regional association plots of 5 suggestive loci ($p < 1$x10^{-6}) for intact TAFI: (**A**) TMEM232 locus, (**B**) TBX5/RBM19 locus, (**C**) SNTG2/TPO locus, (**D**) DENR/CCDC62 locus, and (**E**) SEMA5A locus. SNPs are plotted by chromosomal location (x-axis) and association to intact TAFI concentrations ($-\log_{10} P$ value; left y-axis). The colors reflect linkage disequilibrium of each SNP with the top SNP at the locus, and recombination rates (from 1000 Genomes, phase 3; right y-axis) are shown to reflect local linkage disequilibrium structure. The P value for the top SNP is represented by a purple diamond.
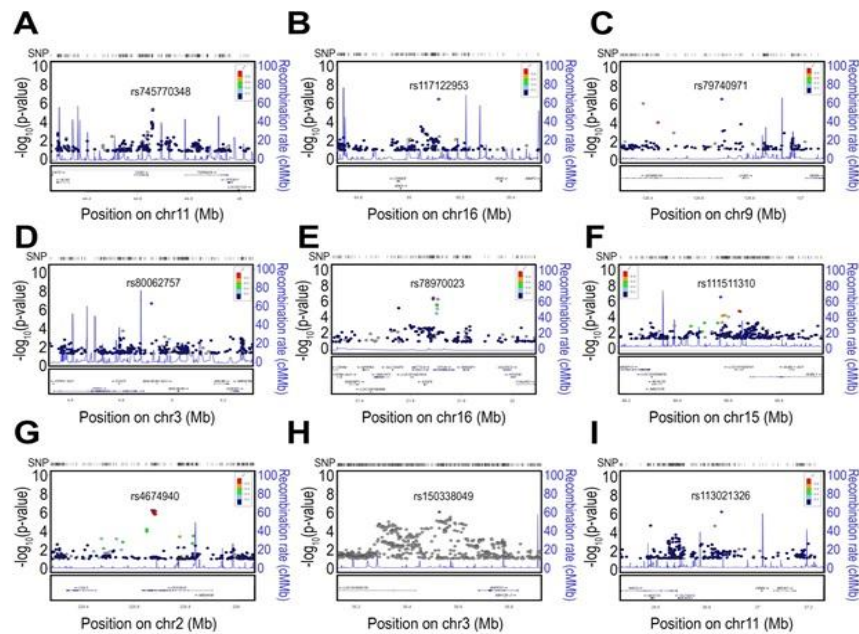
Supplementary Figure S2 Regional association plots of 9 suggestive loci ($p < 1 \times 10^{-6}$) for TAFI activation peptide (TAFI-AP): (**A**) CD82/TSPAN18 locus, (**B**) IRX5/CRNDE locus, (**C**) DENND1A/LHX2 locus, (**D**) BHLHE40 locus, (**E**) OTOA locus, (**F**) LOC101929701 locus, (**G**) DOCK10 locus, (**H**) ARPP21/MIR128–2 locus, and (**I**) FIBIN/SLC5A12 locus. SNPs are plotted by chromosomal location (x-axis) and association to TAFI-AP concentrations ($-\log_{10} P$ value; left y-axis). The colors reflect linkage disequilibrium of each SNP with the top SNP at the locus, and recombination rates (from 1000 Genomes, phase 3; right y-axis) are shown to reflect local linkage disequilibrium structure. The P value for the top SNP is represented by a purple diamond.